

-104-

WHAT IS CLAIMED IS:

1. (1021 & 2471) A binding composition which specifically and/or selectively binds TGF Beta 1 isoform over TGF Beta 2 and/or TGF Beta 3 and which neutralizes TGF Beta 1 comprising at least one binding site comprising:
 - a) at least four contiguous amino acids from QQWNGNPPA (SEQ ID NO: 24)(VL CDR3);
 - b) at least six contiguous amino acids from QQWDSNPPA (SEQ ID NO: 27)(VL CDR3);
 - 10 c) at least five contiguous amino acids from YIYPYNGDTGYNQKFKS (SEQ ID NO: 14), wherein one of said at least five contiguous amino acids is D (VH CDR2); or
 - d) at least five contiguous amino acids from GYYWFAY (SEQ ID NO: 15) (VH CDR3);or
- 15 (3821) a binding composition which specifically and/or selectively binds human TGF Beta 1 isoform over TGF Beta 2 and/or TGF Beta 3 and which neutralizes TGF Beta 1 comprising at least one antibody binding site comprising:
 - a) at least six contiguous amino acids from LQYASSPYT (SEQ ID NO: 20) 30)(VL CDR3);
 - b) at least five contiguous amino acids from GYTFTDYTMH (SEQ ID NO: 19)(VH CDR1);
 - c) at least eight contiguous amino acids from LITPFYGDALYNQKFKG (SEQ ID NO: 20)(VH CDR2); or
 - 25 d) at least seven contiguous amino acids from GGLRRGPPFAY (SEQ ID NO: 21)(VH CDR3).
2. The binding composition of Claim 1 further comprises an additional binding site selected from the following:
 - a) RASSSVSYM (SEQ ID NO: 22)(1021 VL CDR1);
 - 30 b) ATSNLAS (SEQ ID NO: 23)(1021 VL CDR2);

-105-

- c) GYTFTDYNMH (SEQ ID NO: 13)(1021 VH CDR1);
- d) RASQEISGYLS (SEQ ID NO: 28)(3821 VL CDR1);
- e) ATSSLDS (SEQ ID NO: 29)(3821 VL CDR2); and
- f) GYTFTDYTMH (SEQ ID NO: 19)(3821 VH CDR1).

5 3. The binding composition of Claim 2 comprising:

- a) at least three said binding sites;
- b) at least four said binding sites;
- c) at least five said binding sites;
- d) at least six said binding sites; or
- 10 e) at least seven said binding sites.

4. The binding composition of Claim 3, wherein:

a) said binding site:

- i) is specifically immunoreactive with mature human TGF Beta-1;
- ii) is specifically immunoreactive with mature murine TGF Beta-1;
- 15 iii) is raised against a purified or recombinantly produced human TGF
Beta-1 protein or fragment thereof;
- iv) is in a monoclonal antibody, Fab, Fv, scFv, F(ab)2, or a variable
domain of an antibody;
- v) has at least one, two, or three conservative substitutions; or
- 20 vi) is in a human or a humanized antibody framework; or

b) said binding composition:

- i) is an antibody molecule;
- ii) is a monoclonal antibody molecule;
- iii) is a diabody molecule;
- 25 iv) is a triabody molecule;
- v) is a tetrabody molecule;
- vi) is a minibody molecule;
- vii) is a monoclonal antiserum;
- viii) is detectably labeled;
- 30 ix) is lyophilized;
- x) is sterile; or

-106-

xi) is in a buffered composition.

5. The binding composition of Claim 4 that is a monoclonal antibody, wherein said monoclonal antibody comprises at least one sequence at a CDR1, CDR2, or CDR3 of the light chain variable region (LCVR); or at a CDR1, CDR2, or CDR3 of the heavy chain variable region (HCVR) selected from:

- a) GYTFTDYNMH (SEQ ID NO: 13)(1021 VH CDR1);
b) RASSSVSYM (SEQ ID NO: 22)(1021 VL CDR1);
c) YIYPYNGDTGYNQKFKS (SEQ ID NO: 14)(1021 VH CDR2);
d) ATSNLAS (SEQ ID NO: 23) (1021 VL CDR2);
e) GYYWFAY (SEQ ID NO: 15) (1021 VH CDR3);
f) QQWNGNPPA (SEQ ID NO: 24)(1021 VL CDR3); or
g) QQWDSNPPA (SEQ ID NO: 27)(2471 VL CDR3).

6. The monoclonal antibody of Claim 5 wherein said CDR2 of the light chain variable region (LCVR) is ATSNPASYK or F (SEQ ID NO: 23) (2471 VL CDR2).

7. The monoclonal antibody of Claim 6 wherein said CDR2 of the heavy chain variable region (HCVR) is YIYPYDGETGYNQKFKS (SEQ ID NO: 14)(2471 VH CDR2).

8. The monoclonal antibody of Claim 7, wherein said CDR1 of the light chain variable region (LCVR) is RASSSVSYM (SEQ ID NO: 22)(1021 VL CDR1).

9. The monoclonal antibody of Claim 8, wherein said CDR1 of the heavy chain variable region (HCVR) is GYTFTDYNMH (SEQ ID NO: 13)(1021 VH CDR1).

10. The monoclonal antibody of Claim 9 wherein said CDR3 of the light chain variable region (LCVR) is QQWNGNPPA (SEQ ID NO: 24)(1021 VL CDR3).

-107-

11. The monoclonal antibody of Claim 10 wherein said CDR3 of the heavy chain variable region (HCVR) is GYYWFAY (SEQ ID NO: 15) (1021 VH CDR3).

12. The monoclonal antibody of Claim 11, wherein said light chain variable region comprises at least 10 contiguous residues of SEQ ID NO: 2

5 (QIVLTQSPAIMASAPGEKVTMTCRASSSVSYMHWYQKPGSSPKPWI
YATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQQWNGNPP
AFGGGTKLEIKRA).

13. The monoclonal antibody of Claim 12, wherein said heavy chain variable region comprises at least 10 contiguous residues of SEQ ID NO: 4

10 (PELVKPGASVKISCKASGYTFTDYNMHWVKQSHGKSLEWLGYIYPY
NGDTGYNQFKFSKATLTVDNSSSTAYMELRSLTSEDSAVYYCVRGYY
WFAYWGRGTLVTVST).

14. The monoclonal antibody of Claim 13 that:

- 15 a) is humanized;
- b) comprises of human or humanized constant regions;
- c) is a Fab fragment;
- d) is an Fv fragment;
- e) is a scFv fragment;
- f) is a F(ab)₂ fragment;
- 20 g) is detectably labeled;
- h) is lyophilized;
- i) is encoded in an isolated nucleic acid molecule;
- j) is encoded in an isolated nucleic acid molecule that is operably linked
in an expression vector;
- 25 k) is encoded in an isolated nucleic acid molecule that is operably linked
in an expression vector that is incorporated into a host cell;
- l) is a chimeric antibody;
- m) is conjugated to another chemical moiety;
- n) is sterile;

-108-

o) is a pharmaceutical composition;

15. The monoclonal antibody of Claim 11, wherein said CDR1, CDR2, and CDR3 of said heavy variable region and said CDR1, CDR2, and CDR3 said light chain variable region are embedded within a human or humanized framework.

5 16. The monoclonal antibody of Claim 15, wherein said framework is human or humanized.

17. The monoclonal antibody of Claim 15 that:

a) is a Fab fragment;

b) is an Fv fragment;

10 c) is an scFv fragment;

d) is a F(ab)2 fragment;

e) is fused to a human constant region;

f) is conjugated to another chemical moiety;

15 g) comprises a heavy chain constant region selected from: IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM, and IgD;

h) comprises a human light chain constant region;

i) is detectably labeled;

j) is lyophilized;

k) is a fusion protein;

20 l) is sterile; or

m) comprises a pharmaceutical composition.

18. The binding composition of Claim 4 that is a monoclonal antibody, wherein said monoclonal antibody comprises at least one sequence at a CDR1, CDR2, or CDR3 of the light chain variable region (LCVR); or at a CDR1, CDR2, or CDR3 of the heavy chain variable region (HCVR) selected from:

a) RASQEISGYLS (SEQ ID NO: 28)(3821 VL CDR1);

b) ATSSLDS (SEQ ID NO: 29)(3821 VL CDR2);

25 c) LQYASSPYT (SEQ ID NO: 30)(3821 VL CDR3);

-109-

- d) GYTFTDYTMH (SEQ ID NO: 19)(3821 VH CDR1);
- e) LITPFYGDALYNQKFKG (SEQ ID NO: 20)(3821 VH CDR2); and
- f) GGLRRGPPFAY (SEQ ID NO: 21)(3821 VH CDR3).

- 5 19. The monoclonal antibody of Claim 18 wherein said CDR2 of the light chain variable region (LCVR) is ATSSLDS (SEQ ID NO: 29) (3821 VL CDR2).
20. The monoclonal antibody of Claim 19 wherein said CDR2 of the heavy chain variable region (HCVR) is LITPFYGDALYNQKFKG (SEQ ID NO: 20)(3821 VH CDR2).
- 10 21. The monoclonal antibody of Claim 20, wherein said CDR1 of the light chain variable region (LCVR) is RASQEISGYLS (SEQ ID NO: 28) (3821 VL CDR1).
22. The monoclonal antibody of Claim 21 wherein said CDR1 of the heavy chain variable region (HCVR) is GYTFTDYTMH (SEQ ID NO: 19)(3821 VH CDR1).
- 15 23. The monoclonal antibody of Claim 22 wherein said CDR3 of the light chain variable region (LCVR) is LQYASSPYT (SEQ ID NO: 30)(3821 VL CDR3).
24. The monoclonal antibody of Claim 23 wherein said CDR3 of the heavy chain variable region (HCVR) is GGLRRGPPFAY (SEQ ID NO: 21)(3821 VH CDR3).
- 20 25. The monoclonal antibody of Claim 24, wherein said light chain variable region comprises residues 21-129 of SEQ ID NO: 10
(DVQITQSPSSLSASLGERVSLTCRASQEISGYLSWLQKPDGTIKRLIY
ATSSLDSGVPKRFSGSRSGSDYSLTISSPESEDFVDYYCLQYASSPYTFG
GGTKLEIKRA).

-110-

26. The monoclonal antibody of Claim 25, wherein said heavy chain variable region comprises residues 29-140 of SEQ ID NO: 12
(AALMRPGVSVKISCKGSGYTFTDYTMHWVKQSHAKSLEWIGLITPFY
GDAIYNQKFKGKATMTVDKSSSTAYMELARLTSDDSAIYYCTRGLR
RGPPFAYWGQGTLLTVSA).

27. The monoclonal antibody of Claim 26 that is:

- a) humanized;
- b) fused to a human constant region;
- c) a Fab fragment;
- d) an Fv fragment;
- e) a scFv fragment;
- f) a F(ab)₂ fragment;
- g) detectably labeled;
- h) lyophilized;
- i) a chimeric antibody;
- j) used in the manufacture of a medicament for administration to a mammal for the treatment of a fibrotic condition selected from:
 - k) conjugated to another chemical moiety;
 - l) sterile; or
 - m) a pharmaceutical composition.

28. The monoclonal antibody of Claim 24, wherein said CDR1, CDR2, and CDR3 of said heavy variable region and said CDR1, CDR2, and CDR3 said light chain variable region are linked within a human or humanized framework.

29. The monoclonal antibody of Claim 28 that:

- a) is a Fab fragment;
- b) is an Fv fragment;
- c) is an scFv fragment;
- d) is a F(ab)₂ fragment;

-111-

- e) is fused to a human constant region;
- f) is conjugated to another chemical moiety;
- g) comprises a heavy chain constant region selected from: IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM, and IgD;
- h) comprises a human light chain constant region;
- i) is detectably labeled;
- j) is a fusion protein;
- k) is lyophilized;
- l) is sterile; or
- m) comprises a pharmaceutical composition.

30. A method of using the binding composition of Claim 3, comprising contacting said binding composition with a biological sample comprising an antigen, thereby forming a TGF Beta 1 binding composition:antigen complex.

31. The method of Claim 30, wherein said biological sample is from a human, and wherein said binding composition is an antibody.

32. A detection kit comprising said binding composition of Claim 3, and:
a) instructional material for the use of said binding composition for said detection;
or
b) a compartment providing segregation of said binding composition.